Unexpected halogen exchange with halogenated solvents in the iron(III) promoted oxa-alkyne and aza-alkyne Prins cyclizations

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Dedicated to Prof. Dr. Joan Bosch on his 60th Anniversary

Abstract
An unexpected halide exchange with halogenated solvents using iron(III) halides as promoters in oxa- and aza-alkyne Prins cyclizations have been observed. The process is specific for alkynes, while during the Prins cyclization using both homoallylic alcohols and *N*-tosyl amines, the halide participation from the halogenated solvent was absent. Calculation at *ab initio* level provides substantiation of the proposed model.

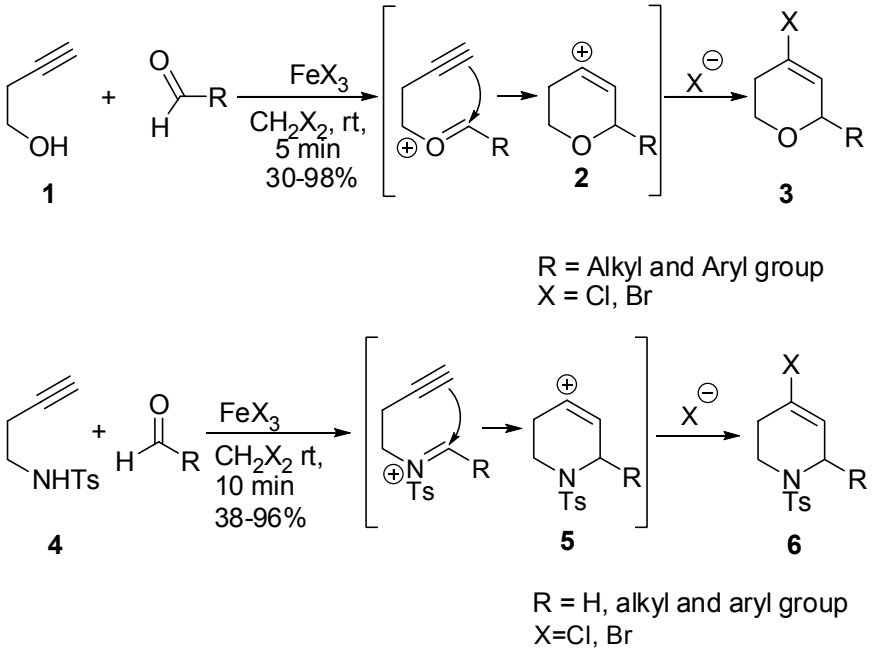
Keywords: Prins cyclization, aza-Prins cyclization, Fe(III) halides, vinyl cations, halogen abstraction

Introduction

The coupling between olefins and aldehydes induced by Lewis acid, known as the *Prins* reaction,[1] has been extensively applied to the synthesis of many natural products containing cyclic compounds in their structures.[2,3] The Prins cyclization is a powerful method to access substituted tetrahydropyrans.[4,5] The aza-Prins cyclization is the nitrogen version used to obtain substituted azacycles.[6] Usually this reaction generates an unsaturated cation intermediate, which suffers further cyclization, through oxa-Prins or aza-Prins reactions, leading to the corresponding six membered cyclic product. There are several examples that involve an intramolecular attack of a nucleophilic olefin with an iminium cation or oxocarbenium cation which leads to the formation of a heterocyclic ring system. However, cyclization reactions of alkynes, with weak electrophiles such as iminium ions, have received less attention.[7,8]

We recently found a new Prins-type cyclization between homopropargylic alcohol and aldehydes in the presence of inexpensive, environmentally friendly, and stable iron(III) halides to obtain 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans **3** (Scheme 1).[9] Recently, we explored the use of

iron(III) halides to generate six-membered azacycles. The coupling between homopropargyl tosyl amines with aldehydes provides 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines **6** in good yields (Scheme 1).[10] A critical issue in these reactions is the choice of suitable solvent. We found, in the above two procedures, an unexpected halide exchange with halogenated solvents presumably caused by the vinyl cation intermediates **2** and **5**.



Scheme 1. Synthesis of 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrand and 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines.

Only a few examples of halogen abstraction by vinyl cations from chlorinated solvents have been described. In 1968, White and coworkers described the abstraction of a chloride ion from methylene chloride by the 1-norbornyl cation. The authors reported that the deamination of l-norbornylamine by means of the *N*-nitro carbamate and *N*-nitro amide decomposition yields reactive carbocations that can be intercepted by relatively inert solvents such as chloroform and benzene.[11]

Later, in 1972, Johnson examined the fate of vinyl cations, resulting from biomimetic polyene cyclizations, in the presence of various halogenated solvents as sources of nucleophiles, using trifluoroacetic acid.[12,13] Almost at the same time, Landsbury and coworkers described the same phenomenon, in a model study for steroid C/D ring synthesis.[14] In 1995, Curran and coworkers proposed a vinyl cation as a possible intermediate responsible for the abstraction of a chloride ion from CH_2Cl_2 during the synthesis of an alkynylcyclopentane-1,3-dione.[15]

In the last years, a few examples of halogen abstraction by vinyl cations from chlorinated solvents has been reported; Kozmin and coworkers in the cyclizations of 1-siloxy-1,5-diynes promoted by Brønsted acids ($HNTf_2$),[16] and Cook and coworkers in the atom transfer cyclization

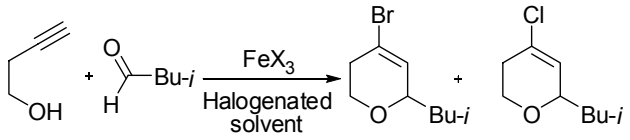
catalyzed by $InCl_3$.[17] Cook proposed that the reaction appears to proceed via a cationic halogen activation mechanism with halogen transfer from the solvent or from the substrate.

In light of these precedents, we were very interested in exploring the scope and limitations of the halogen exchange during the oxa- and aza-alkyne Prins cyclization, and developing a possible explanation for the phenomena. In this manuscript, we report on such studies including *ab initio* theoretical calculations that support our model.

Results and Discussion

The oxa-alkyne Prins cyclization takes place between homopropargylic alcohol and aldehydes providing 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans in good yields (Scheme 1). The reaction is applicable to both aromatic and aliphatic substrates, as well as with both enolizable and nonenolizable aldehydes. It is noteworthy that the carbon-carbon formation is very rapid, being usually completed within 5 min. From the different solvents screened (THF, CH_3CN, AcOEt, $CHCl_3$, CCl_4, CH_3NO_2, CH_2Cl_2, and 1,2-dichloroethane) we found the best solvents to be CH_2Cl_2 and 1,2-dichloroethane. However, an unexpected result was the appearance of chlorovinyl derivatives when $FeBr_3$ was used as the promoter and CH_2Cl_2 as the solvent. In an attempt to clarify this point, we ran a reaction using 1,2-dichloroethane as a solvent and obtained a similar amount of the chloro dihydropyran. Our suspicion that the chlorine atom comes from the solvent was clarified by the use of CH_2Br_2 as a solvent, when the uncontaminated bromovinyl ring was cleanly obtained. In a similar manner, the use of $FeCl_3$, in CH_2Br_2, produced the chloro derivative contaminated with the corresponding bromide (Table 1). The same effect was observed when $InBr_3$ in CH_2Cl_2 was used as Lewis acid.

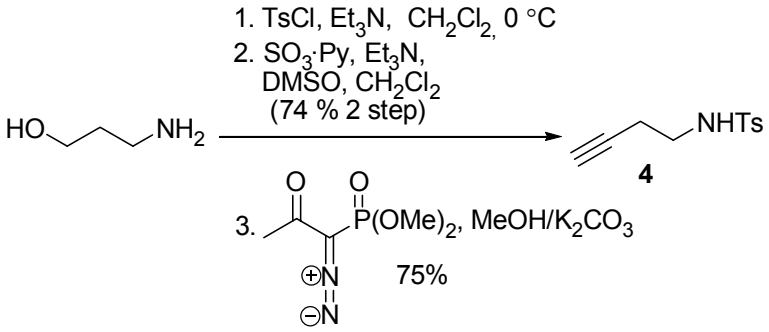
Table 1. Participation of the halogenated solvent as source of the halogen in the oxa-alkyne Prins cyclization



1 **3a** **3b**

Entry	Lewis acid	Solvent	Global yield (%)	Ratio **3a**:**3b**
1	$FeBr_3$	CH_2Cl_2	94	50:50
2	$FeBr_3$	$ClCH_2CH_2Cl$	93	50:50
3	$FeBr_3$	CH_2Br_2	95	100:0
4	$FeCl_3$	CH_2Cl_2	90	0:100
5	$FeCl_3$	CH_2Br_2	94	50:50
6	$InBr_3$	CH_2Cl_2	94	50:50
7	$InBr_3$	CH_2Br_2	93	100:0

Alternatively, the aza-Prins alkyne cyclization uses homopropargyl tosyl amines and takes into account the similar chemical reactivity of the sulfonamide nitrogen and the alcohol. Homopropargyl tosyl amines are not commercially available and must be synthesized. The *N*-(but-3-ynyl)-4-methylbenzenesulfonamide (**4**) was readily prepared from 3-aminopropan-1-ol in three steps, using the Ohira methodology (Scheme 2).[18] N-Tosylation and Parek-Doehring oxidation produced the corresponding aldehyde in 74% yield. With this aldehyde in hand, we applied the Ohira conditions to obtain the *N*-(but-3-ynyl)-4-methylbenzenesulfonamide (**4**) in 75% yield.



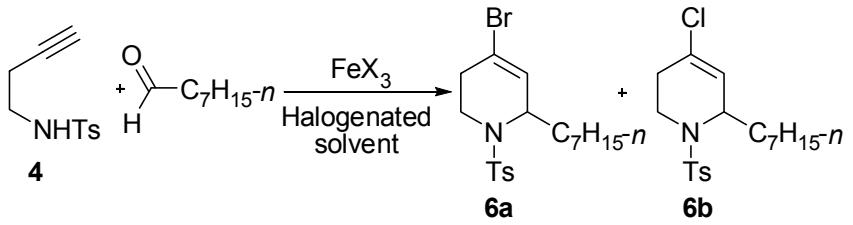
Scheme 2. Synthesis of *N*-(but-3-ynyl)-4-methylbenzenesulfonamide (**4**).

The coupling between homopropargyl tosyl amines and aldehydes promoted by iron (III) halides, generates a γ,δ-unsaturated-iminium intermediate, which after cyclization through an alkyne aza-Prins reaction, provides 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines in good yields (Scheme 1). Like the oxa-Prins cyclization, the reaction proceeds satisfactorily with aromatic and aliphatic substrates, as well as with enolizable and nonenolizable aldehydes. In addition, the carbon-carbon bond formation is very rapid even at 0 °C, being usually complete within 10 min and the *N*-sulfonyliminium intermediated are readily generated in situ.

A similar solvent effect to that reported for the oxa-alkyne Prins cyclization was observed. When $FeBr_3$ was used as catalyst and the reaction run with CH_2Cl_2 as solvent, the corresponding piperidine derivative was obtained in a mixture with the bromovinyl compound (Table 2). The halogen exchange from halogenated solvents, in both oxa-alkyne and aza-alkyne Prins cyclization, is not dependent of the nature of the aldehyde. We have carried out the cyclization reaction with different kind of aldehydes observing always the same solvent effect.

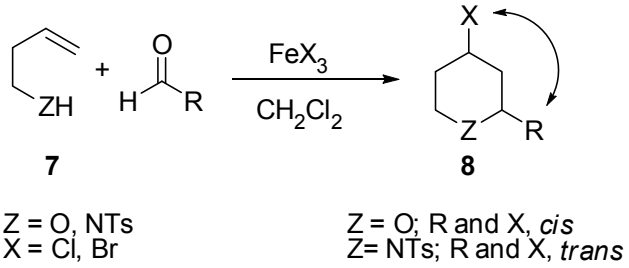
With these results in hand and to determine the influence of the amount of iron(III) halides used, we decided to run the reaction using substoichiometric amounts of $FeCl_3$ (0.1, 0.3, 0.5 equiv.) and using CH_2Cl_2 as solvent as possible source of chloride ion. Unfortunately, the reaction depends directly on the amounts of iron(III) halide used, stoichiometric amounts of this salt are required to obtain a total conversion of the halide exchange. These results suggest that vinyl cation intermediates **2** and **5** are formed and are responsible of the halide exchange.

Table 2. Participation of the halogenated solvent as source of the halogen in the alkyne aza-Prins cyclization



Entry	Lewid Acid	Solvent	Global Yield (%)	Ratio **6a**:**6b**
1	$FeBr_3$	CH_2Cl_2	97	85:15
2	$FeBr_3$	CH_2Br_2	96	100:0
3	$FeCl_3$	CH_2Cl_2	97	0:100
4	$FeCl_3$	CH_2Br_2	81	50:50

Interestingly, we did not observed mixtures of halogenated products (**8**, X = Cl or Br) when the oxa- and aza-Prins cyclizations were performed over homoallyl alcohol and homoallyl tosyl amine (**7**, Z = O, NTs), respectively (Scheme 3).



Scheme 3. Oxa- and aza-Prins cyclizations catalyzed by iron(III) halides.

Several hypotheses could be considered to explain the observed results: a) halide exchange occurs between the halogenated solvent and the metal,[19] b) capture of the solvent halogen by the vinyl cation intermediate,[15-17] and c) a combination of both a and b.

To provide evidence to support a possible mechanism, some calculations at the "ab initio" level were performed on the interaction of the $FeCl_3$ and the CH_2Cl_2. The theoretical study for such interaction is not trivial. It involves weak bonds that require a relatively large basis set system with diffuse functions to be described, and taking into account the electron correlation. Considering the above, we performed some "ab initio" calculation for CH_2Cl_2, $FeCl_3$ and CH_2Cl_2…$FeCl_3$ complex using for geometry optimizations the mixed functional B3LYP/6-31G* basis set and pseudopotential basic set LACVP*.[20] When studying weak interactions between molecules, it is necessary to be extremely careful since a minimum in the potential energy surface does not guarantee a "true bond". The method "Atoms in Molecules" (AIM) of Bader

and co-workers,[21] solves this problem. The method is based on the careful analysis of the electronic density topology and generates appropriate molecular graphs, representing a network of bond paths. A bond path is a pair of special gradient density paths linking a nucleus with a bond critical point (saddle point in ρ corresponding to a minimum value on the molecular axis between the two nuclei and a maximum in a direction perpendicular to this axis). Such graphs can be considered as the AIM definition of the bond. If and only if two atoms are linked by a bond path are they bonded to one another.

To start the Bader analysis we needed to compute a good electronic density since the pseudopotential basis sets cannot be used to obtain it. We performed a single-point energy calculation over previous optimized geometries, using B3LYP/TZV for all of the atoms involved. AIM analysis showed a CH_2Cl_2-$FeCl_3$ complex as a stable structure (Figure 1). This figure shows the most relevant structural features for the complex.

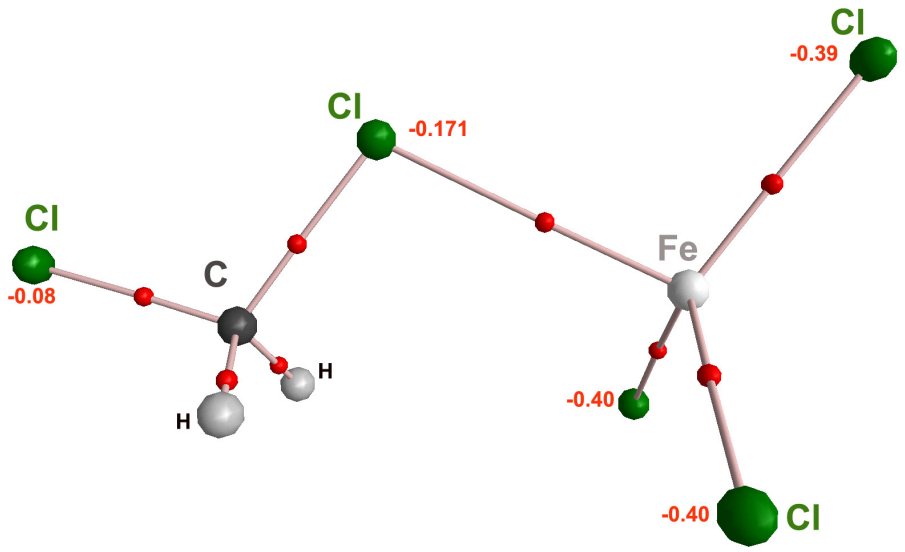
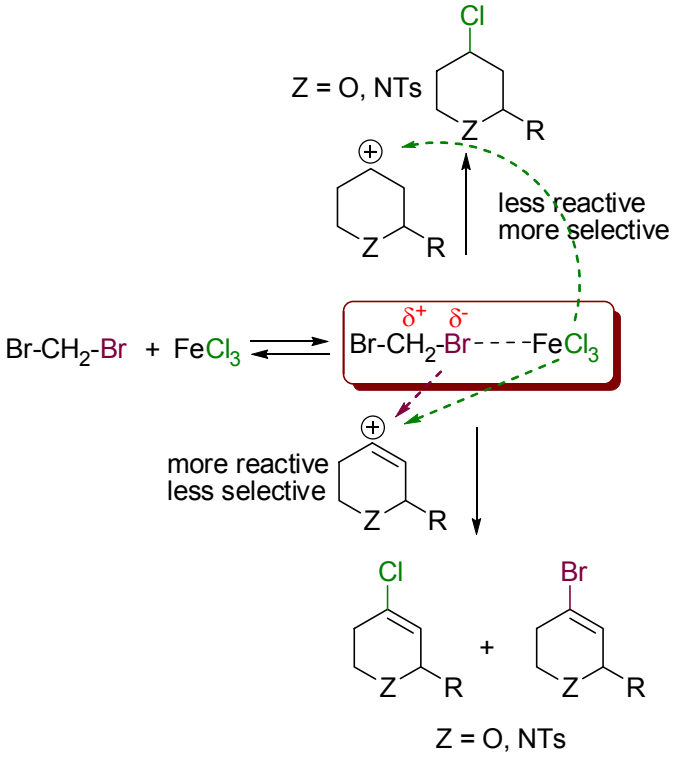


Figure 1. Molecular graph corresponding to complex between $FeCl_3$ and CH_2Cl_2. Small dots into bond paths are the bonds critical points. The charged are indicated by red values.

The analysis of charge distribution can show the electrophilic nature of $FeCl_3$ in this association. However, it is well recognized that the concept of atomic charge in a molecule is difficult to define because it is not related to a true physical quantity and, therefore, it is not rigorously defined in quantum mechanics. The essence of the AIM theory is the definition of an atom as it exists in the molecule. We can then find atomic charges, without the problems related to electronic distributions based on orbital methods, by simple integration of electronic density over the well-defined atomic basins. An increase of the charge in chlorine associate to metal is observed (from -0.08 to -0.171) as well as a weakness in the C-Cl bond. Presumably, the halide

associated with the two electrophilic entities may be transferred to a highly reactive intermediate such the vinyl cation.[22]

In light of these results, we postulate the overall model outlined in Scheme 4 for cyclization reactions using $FeCl_3$ as promoter and CH_2Br_2 as solvent. If we assume an association between CH_2Br_2 and $FeCl_3$, we obtain a complex where the bromine atom is more electron-rich being the C-Br bond weaker. The presence of the more reactive vinyl cation promotes the bromine abstraction from the CH_2Br_2. In the case of the secondary carbocation it is not reactive enough to promote the abstraction of the bromine, leading cleanly to the chloro-heterocycle as the sole product.



Scheme 4. Plausible model for the halogen abstraction from halogenated solvents in the oxa-alkyne and aza-alkyne Prins cyclizations promoted by $FeCl_3$ in CH_2Br_2 as solvent.

In conclusion, we have examined the fate of vinyl cations, resulting from oxa-alkyne and aza-alkyne Prins cyclizations, in the presence of various halogenated solvents as sources of halides, using iron (III) halides as promoter. Experiments with Prins cyclizations and ab inito calculations are the base of a model that rationalizes those reactions in which the complex formation between the halogenated solvent and the iron(III) halides is the activating step. The stronger reactivity of the vinyl cations is the responsible for the halogen abstraction from the solvent. From the synthetic point of view, it is clear that to avoid mixtures for each halide the corresponding halogenated solvent must be used.

Experimental Section

General Procedures. ^{1}H and ^{13}C-NMR spectra were recorded at 25 °C on a Bruker Avance-400 and/or 300 spectrometer in $CDCl_3$ as solvent, and chemical shifts are reported relative to Me_4Si. Low- and high-resolution mass spectra were taken using a Micromass Autospec spectrometer. Elemental analyses were performed on a Fisons Instruments EA 1108 CHNS-O. Optical rotations were determined for solutions in chloroform or *n*-hexane with a Perkin-Elmer Model 241 polarimeter. Infrared spectra were recorded on a Bruker IFS 55 spectrophotometer. Column chromatography was performed on Merck silica gel, 60 Å and 0.2–0.5 mm. Visualization of spots was performed with UV light and/or phosphomolybdic acid in ethanol stain, and/or ninhydrin (10% w/v in EtOH), and/or vanillin in EtOH:H_2SO_4:HOAc (15:1:1.3). All solvents were purified by standard techniques.[23] Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

General procedure for the ferric halide promoted oxa-Alkyne Prins cyclization. To a stirred solution of homopropargylic or homoallylic alcohol (1 equiv) and aldehyde (1 equiv) in dry CH_2Cl_2 was added anhydrous FeX_3 (1 equiv) in one portion at room temperature. The reaction was complete in approximately 1 min, quenched by addition of water with stirring for 5 min, and extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

Typical experimental procedure for the ferric halide promoted alkyne aza-Prins cyclization. To a solution of homoallyl tosyl amine or homopropargyl tosyl amine (1 equiv) and aldehyde (1.5 equiv) in dry CH_2X_2 was added anhydrous FeX_3 (1.5 equiv) in one portion. The reaction was concluded in approximately 10 min, quenched by addition of water and extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

4-Bromo-5,6-dihydro-2-isobutyl-2*H*-pyran (3a). ^{1}H NMR ($CDCl_3$) δ 0.89 (dd, J = 1.2, 6.5 Hz, 6H), 1.24 (m, 1H), 1.49 (m, 1H), 1.78 (m, 1H), 2.28 (brs, 1H), 2.65 (m, 1H), 3.65 (m, 1H), 3.96 (m, 1H), 4.10 (brs, 1H), 5.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1 (CH_3), 23.2 (CH_3), 24.3 (CH_2), 35.2 (CH_2), 43.8 (CH_2), 64.1 (CH_2), 74.0 (CH), 118.2 (C), 131.7 (CH); IR ($CHCl_3$) (cm^{-1}) 2958, 2929, 2868, 1651, 1339, 1105, 796; MS *m/z* (rel. intensity) 162 $(M - C_4H_9)^+$ (67), 139 $(M - Br)^+$ (100), 82 (37); Anal. Calcd. for $C_9H_{15}BrO$: C, 49.33; H, 6.90. Found: C, 49.33; H, 7.28. **4-Chloro-5,6-dihydro-2-isobutyl-2*H*-pyran (3b)**. ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6H), 1.25 (m, 1H), 1.51 (m, 1H), 1.80 (sep, J = 6.5 Hz, 1H), 2.17 (brs, 1H), 2.56 (m, 1H), 3.67 (m, 1H), 4.00 (m, 1H), 4.14 (brs, 1H), 5.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1 (CH_3), 23.2 (CH_3), 24.3 (CH_2), 33.0 (CH_2), 44.5 (CH_2), 63.6 (CH_2), 73.1 (CH), 127.4 (CH), 129.3 (C); IR ($CHCl_3$) (cm^{-1}) 2961, 1672, 1465, 1079; MS *m/z* (rel. intensity) 139 $(M - Cl)^+$ (36), 117 (100); Anal. Calcd. for $C_9H_{15}ClO$: C, 61.89; H, 8.66. Found: C, 61.93; H, 8.65.

Dimethyl 1-diazo-2-oxopropylphosphonate. To a stirred suspension of NaH (264.8 mg at 60%)[24] in THF:C_6H_6 (5:1, 12 mL) at 0 °C were added *p*-toluenesulfonyl azide[25] (1.29 g, 6.6 mmol) and dimethyl 2-oxopropylphosphonate (0.83 mL, 6.0 mmol), respectively. The reaction wad allowed to proceed for 12 hours at room temperature and then filtered through a pad of Celite to lead the pure Dimethyl 1-diazo-2-oxopropylphosphonate (1.05 g, 5.5 mmol) in 90% yield.

***N*-(But-3-ynyl)-4-methylbenzenesulfonamide (4).** To a solution of 3-aminopropan-1-ol (5.10 mL, 66.6 mmol) in CH_2Cl_2 (166 mL) at 0 °C were added Et_3N (18.56 mL, 133.1 mmol) and 4-methylbenzene-1-sulfonyl chloride (66.6 mL, 66.6 mmol) respectively. The reaction wad allowed to warm to rt. The reaction was diluted with CH_2Cl_2 and washed with H_2O, dried over $MgSO_4$ and concentrated. The crude obtained was used in the next reaction.

To a solution of the alcohol crude in CH_2Cl_2 (500 mL) at 0 °C were added Et_3N (65.2 mL, 467.0 mmol) and DMSO (43.8 mL, 61.7 mmol) respectively. The mixture was stirred for 15 min, and SO_3·Py (31.8 g, 199.7 mmol) was slowly added. The reaction was diluted with CH_2Cl_2 and washed with a HCl aqueous solution (5% w/v), a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude obtained was purified through a flash column of silica gel (*n*-hexane/EtOAc, 80:20) and the aldehyde (11.3 g, 49.9 mmol, 75% 2 steps) was used in the next reaction.

To a stirred solution of the aldehyde (2g, 8.8 mmol) in MeOH (88.0 mL) were added sequentially K_2CO_3 (2.4 g, 17.8 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (2.0 g, 10.6 mmol) at rt. The reaction was stirred until TLC showed the end of the reaction. The mixture of reaction was filtered through a pad of Celite and concentrated. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc 40:60) to give *N*-(but-3-ynyl)-4-methylbenzenesulfonamide (1.4 g, 6.4 mmol) in 72% yield as an oil.[26] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.88 (s, 1H), 3.10 (dd, *J*= 6.48, 13.0 Hz, 2H), 2.43 (s, 3H), 2.33 (m, 2H), 1.99 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6 (C), 137.0 (C), 129.7 (2CH), 127.2 (2CH), 80.3 (C), 70.9 (CH), 41.6 (CH_2), 21.5 (CH_3), 19.8 (CH_2).

4-Bromo-2-heptyl-1,2,5,6-tetrahydro-1-tosylpyridine (**6a**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 9.6 Hz, 2H), 6.01 (brs, 1H), 4.32 (brs, 1H), 3.85 (dd, *J* = 6.0, 14.7 Hz, 1H), 3.24 (ddd, *J* = 5.0, 11.4, 16.1 Hz, 1H), 2.42 (s, 3H), 2.15 (m, 1H), 2.06 (dd, *J* = 4.7, 18.5 Hz, 1H), 1.54 (m, 3H), 1.33 (m, 9H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5 (C), 137.9 (C), 129.6 (2CH), 129.3 (C), 126.9 (2CH), 119.1 (C), 55.7 (CH), 39.4 (CH_2), 34.5 (CH_2), 32.7 (CH_2), 31.7 (CH_2), 29.3 ($2CH_2$), 29.1 (CH_2), 26.0 (CH_2), 22.6 (CH_2), 21.5 (CH_3), 14.1 (CH_3). IR ($CHCl_3$) (cm^{-1}) 2927, 2856, 1340, 1160, 1095 cm^{-1}. Anal. Calcd. for $C_{19}H_{28}BrNO_2S$ calcd.: C 55.07 H 6.81 N 3.38; found: C 55.26 H 7.07 N 3.36.

4-Chloro-2-heptyl-1,2,5,6-tretrahydro-1-tosylpyridine (**6b**). ^{1}H NMR ($CDCl_3$, 300 MHz)δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 6.7 Hz, 2H), 5.78 (brs, 1H), 4.37 (brs, 1H), 3.89 (dd, *J* = 6.2, 14.7 Hz, 1H), 3.22 (ddd, *J* = 4.9, 11.6, 16.3 Hz, 1H), 2.42 (s, 3H), 2.05 (m, 1H), 1.93 (dd, *J* = 4.7, 17.4 Hz, 1H), 1.55 (m, 3H), 1.42-1.26 (m, 9H), 0.89 (t, *J* = 6.1 Hz, 3H).^{13}C NMR ($CDCl_3$,

75 MHz) δ 143.4 (C), 137.9 (C), 129.7 (C), 129.6 (2CH), 126.9 (2CH), 125.4 (CH), 54.5 (CH), 38.8 (CH_2), 34.7 (CH_2), 31.7 (CH_2), 30.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 14.0 (CH_3). IR ($CHCl_3$) (cm^{-1}) 2927, 2855, 1458, 1340, 1159 cm^{-1}. Anal. Calcd. for $C_{19}H_{28}ClNO_2S$ calcd.: C 61.69 H 7.63 N 3.79; found: C 61.58 H 7.72 N 3.83.

***cis*-4-Chloro-2-isobutyltetrahydro-2*H*-pyran (8, X = Cl, Z = O, R = Bu-*i*)**. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.98 (m, 2H), 3.34 (m, 2H), 2.06 (m, 2H), 1.78 (m, 2H), 1.50 (m, 2H), 1.18 (m, 1H), 0.99 (m, 6H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ 75.47 (CH), 66.91 (CH_2), 55.88 (CH), 45.07 (CH_2), 43.30 (CH_2), 37.14 (CH_2), 24.23 (CH), 23.11 (CH_3), 22.18 (CH_3). IR ($CHCl_3$) (cm^{-1}) 2958, 2848, 1084, 765. Anal. Calcd. for $C_9H_{17}OCl$ (176.68): C, 61.18; H, 9.70. Found: C, 61.29, H, 9.61.

***cis*-4-Bromo-2-isobutyltetrahydro-2*H*-pyran (8, X = Cl, Z = O, R = Bu-*i*)**. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.10 (m, 1H), 3.93 (m, 1H), 3.33 (m, 2H), 2.65 (m, 2H), 0.85 (m, 6H), 1.16 (m, 1H), 1.44 (m, 1H), 1.72 (m, 2H), 1.98 (q, *J* = 4.7 Hz, 1H ^{13}C NMR ($CDCl_3$, 75 MHz) δ 76.3(CH), 67.8 (CH_2), 46.9 (CH), 45.0 (CH_2), 44.2 (CH_2), 38.0 (CH_2), 24.2 (CH), 23.1 (CH_3), 22.2 (CH_3),. IR ($CHCl_3$) (cm^{-1}) 2957, 2847, 1082, 721**.** Anal. Calcd. for $C_{11}H_{17}OBr$ (221.14): C, 48.88; H, 7.75. Found: C, 48.88, H, 7.75.

***trans*-4-Chloro-2-isobutyl-1-tosylpiperidine (8, X = Cl, Z = Ts, R = Bu-*i*)**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, *J* = 8.3 Hz, 2H) 7.30 (d, *J* = 8.0 Hz, 2H) 4.21 (m, 1H), 4.05 (m, 1H), 3.86 (brdd, *J* = 4.7, 15.0 Hz, 1H), 3.05 (td, *J* = 2.5, 13.3 Hz, 1H), 2.41 (s, 3H), 1.97 (brd, J = 9.8 Hz, 2H), 1.70-1.43 (m, 4H), 1.25 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 Mhz) δ 143.3 (C), 138.0 (C), 129.6 (2CH), 126.9 (2CH), 53.0 (CH), 52.1 (CH), 40.2 (CH_2), 39.2 (CH_2), 38.6 (CH_2), 35.2 (CH_2), 24.7 (CH), 22.5 (CH_3), 22.2 (CH_3), 21.4 (CH_3). IR ($CHCl_3$) (cm^{-1}) 2957, 2870, 1339, 1158, 9352 cm^{-1}. Anal. Calcd. for $C_{16}H_{24}ClNO_2S$ calcd.: C 58.25 H 7.33 N 4.25; found: C 58.26 H 7.53 N 4.32.

***trans*-4-Bromo-2-isobutyl-1-tosylpiperidine (8, X = Br, Z = Ts, R = Bu-*i*)**. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.18 (m, 2H), 3.81 (brdd, *J* = 4.4, 12.6 Hz, 1H), 3.05 (td, *J* = 2.2, 14.7 Hz, 1H), 2.44 (s, 3H), 2.08 (m, 2H), 1.87 (td, *J* = 5.5, 12.8 Hz, 1H), 1.70 (dd, *J* = 4.7, 12.6 Hz, 1H), 1.57 (m, 1H), 1.46 (m, 1H), 1.26 (qui, *J* = 7.1 Hz, 1H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9 (C), 137.6 (C), 129.3 (2CH), 126.5 (2CH), 52.3 (CH), 43.6 (CH), 40.7 (CH_2), 39.1 (CH_2), 38.6 (CH_2), 35.6 (CH_2), 24.3 (CH), 22.1 (CH_3), 21.8 (CH_3), 21.0 (CH_3). IR ($CHCl_3$) (cm^{-1}) 2957, 2870, 1337, 1157, 935 cm^{-1}. Anal. Calcd. for $C_{16}H_{24}$ $BrNO_2S$ calcd.: C 51.34 H 6.46 N 3.74; found: C 51.37 H 6.59 N 3.74.

"Ab initio" computational data

Optimized Structures were performed with Spartan v.1.0.2 using B3LYP/6-31G* basic set and defect pseudopotential (basic set LACVP*). Single point calculation was performed with Gaussian 98W using B3LYP/TZV basic set. The output file WFN was used as input for AIM2000 to perform the analysis "Atom in Molecules" of Bader.

Cartesian coordinates (atomic number, and coordinates x, y, and z in Å) for the complex $CH_2Cl_2 \ldots FeCl_3$

Fe	1.903500	-0.157000	-0.099000
Cl	-0.418500	1.107000	-0.211000
Cl	1.741500	-1.467000	-1.780000
Cl	1.766500	-1.168000	1.780000
Cl	3.276500	1.467000	-0.212000
H	-1.385500	-0.952000	-0.908000
C	-1.599500	-0.283000	-0.078000
H	-1.419500	-0.747000	0.889000
Cl	-3.276500	0.274000	-0.174000

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